

APPLICANTS: Peled, *et al.*

SERIAL NUMBER: 10/774,843

REMARKS

Upon entry of this amendment, claims 401, 411, 414, 416, 419, 422-424, 464-465, 469-471 and 478-480 will be pending in the application.

Independent Claims 401 and 411 have been amended to recite that the culture medium includes each of stem cell factor, thrombopoietin, FLt3 ligand, IL-6 and optionally IL-3. Support for this amendment is found throughout the specification (*See, e.g.* page 25, lines 24-28). No new matter is added.

The Examiner is thanked for the courtesy of a February 17, 2010 Interview where the above amendment was discussed to place the claims in condition for allowance.

Applicants have also submitted a Declaration of Dr. Tony Peled under 37 CFR §1.132 (“2010 Peled Decl.”) which sets forth data confirming that the specifically claimed combination of cytokines produces an expanded CD34+ hematopoietic stem cell population with an increased proportion of CD34+/CD38- and CD34+/Lin- cells in the expanded culture as compared to CD34+ cells cultured in the presence of cytokines and nutrients without exogenously added nicotinamide (as expressly recited in independent claims 401 and 411 – and thus all the claims that depend therefrom).

As discussed in the Interview, the combination of Brown and Block teaches away from the claimed invention. The Examiner concedes that Brown is fatally deficient in failing to disclose the claimed range of nicotinamide concentration. Brown does not suggest to the skilled artisan that the claimed nicotinamide concentration range in serum free media can act as an agent that maintains CD34+ hematopoietic cells in an undifferentiated state and enriches for CD34+/CD38- and CD34+/Lin- cells while the cells are expanded in *ex vivo* culture using a serum-containing culture medium – as claimed here.

Block does not cure the deficiencies of Brown – Block teaches away. Block refers to the use of nicotinamide in the culture/expansion of differentiated hepatocytes – a completely different cell population than the claimed CD34+ hematopoietic stem cell population. Further, none of the cytokines recited in instant claims are present in the Block culture medium. And the ordinarily skilled artisan would not select (out of the many “ingredients” in Block’s culture medium) nicotinamide for use as claimed here. To the contrary, Block teaches the exact opposite – in Block, nicotinamide was used to maintain the differentiated state of the hepatocytes (exactly opposite to the use in the currently claimed invention). *See, Block*, col. 8, lines 26-28. Block also directly teaches away from the use of serum in the culture – as expressly recited in the

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claims here. The entire focus of Block is to provide a chemically defined culture medium that is serum free. *See, e.g.*, col. 1, lines 43-50 and col. 4, lines 8-10.

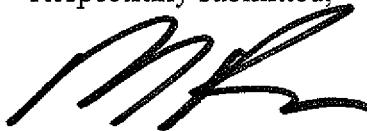
One of ordinary skill in the art combining the teachings of Brown and Block would not, and could not, reach the present invention with predictable results.

The data presented in both the 2010 Peled Decl. (see specifically ¶¶ 4-6, Figures 1 and 2) and the previously submitted 2008 Peled Declaration (pages 2-4 and Figure 1) shows that using nicotinamide in the range of 1.0 mM to 10 mM, as required by the instant claims inhibits differentiation of CD34⁺stem cells (as evidenced by the unexpectedly and substantially increased cell density of undifferentiated CD34+/CD38- and CD34+/Lin- cells), while permitting expansion, *ex vivo*. These unexpected and superior properties are not taught or suggested by the prior art.

CONCLUSION

Applicants submit that the application is in condition for allowance and such action is respectfully requested. However, if upon receipt and review of this amendment, the Examiner believes that the present application is not in condition for allowance and that changes can be suggested which would place the claims in allowable form, the Examiner is respectfully requested to call Applicant's undersigned counsel at the number provided below.

Respectfully submitted,



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Dated: February 22, 2010